

Review Article

Volatile Agents and Liver Transplantation

Ayten Saracoglu^{1*}, Kemal Tolga Saracoglu² and Beliz Bilgili¹¹Department of Anesthesiology and Intensive Care, Marmara University Medical School, Turkey²Department of Anesthesiology and Intensive Care, Health Sciences University Medical School, Turkey

Abstract

Evidence-based scientific data is not enough to conclude the ideal anesthetic technique in liver transplantation. Both total intravenous anesthesia and volatile agents are used. Volatile anesthetic agents cause a reduction of hepatic blood flow. Compound A can be hepatotoxic by transient increase in postoperative liver function tests. Besides, the effect of volatile anesthetics on the incidence of post reperfusion syndrome has not been clarified yet. On the other hand, several studies provide evidence of pharmacologic clinical protective effects of volatile agents on ischemic reperfusion injury in patients undergoing liver resection. It has been demonstrated that preconditioning with desflurane limits NF- κ B activation induced by TNF- α and leading to a cellular protective effect. Desflurane may also inhibit the second phase of the inflammatory response. The effect of hypnotic and volatile agents used during anesthesia on primary graft dysfunction is controversial. In this review, we aimed to discuss the evidence based effects of volatile agents in liver transplantation.

Keywords: Liver transplantation; Volatile agent; Anesthesia

Introduction

Live donor liver transplantation has received a significant interest due to the insufficiency of cadaveric donors. Nowadays, anesthetic regimens used in liver transplantation can be administered in two ways as inhalational or intravenous anesthetic agents according to the preference of anesthetist. However, the effect of hypnotic and volatile agents used during anesthesia on primary graft dysfunction is controversial. Evidence-based scientific data is not enough to conclude which is the best anesthetic technique in this group of patients [1]. Considering the nature of live donor right hepatectomy with the removal of two-thirds of the original liver, it seems important to identify an anesthetic agent with minimal impact on postoperative organ function. In this review, we aimed to discuss the evidence based effects of volatile agents in liver transplantation.

Ischemia Reperfusion Injury (IRI)

Patients with primary graft dysfunction require longer hospitalization and stay in the intensive care unit due to increased complications such as infection and renal dysfunction. This phenomenon greatly decreases survival [2]. However, morbidity and mortality rates have been reduced over the last few years with the reduction of serious postoperative complications such as primary graft dysfunction. Considering the severity of transient changes in hemostasis, metabolism, pharmacokinetics and pharmacodynamics of drugs administered during live donor hepatectomy, significant risks may occur. In addition, the necessity of live donor safety is still

a major concern for the complications. The hepatocyte damage in transplantation occurs as a result of rapid expansion and cooling of the donor organ, prolonged cold storage, hot ischemia time during the transplant procedure, and finally Ischemia-Reperfusion Injury (IRI) [3]. IRI is formed by rapid reperfusion with warm oxygenated blood and resumption of aerobic metabolism. Partial ischemia due to ischemia reperfusion injury in both donor and recipient, and hemodynamic changes caused by the graft after the operation, seriously affect the survival of the graft and sometimes trigger a pathway leading to the graft agent. Hepatocyte injury caused by these ischemic periods can be determined after transplantation. The level of transaminases has normally a peak within 24 hours, and afterwards there is an incrementally decrease in a few days. Lower postoperative Alanine Aminotransferase (ALT) and Total Bilirubin (TB) levels indicate less hepatocyte damage and better liver function. As a result, the severity of ischemia reperfusion injury determines the function of the graft, and primary dysfunction determines both the graft and the patient's early prognosis with the need for retransplantation. Protective approaches against IRI are usually divided into surgical and pharmacological interventions. These interventions are intended to prevent events that lead to cellular damage during pre-conditioning or reperfusion [4]. There are contradictory studies on the superiority of pharmacological agents to each other, and the common opinion is that most of the hepatocyte damage seen in the post-transplant period is caused by IRI [5]. For this purpose, various inhalational anesthetics have been used in live liver donors including desflurane, sevoflurane and isoflurane. The effects of these agents on vital organ functions are still controversial. Besides, the volatile anesthetics have several effects on the expression of adhesion molecules, inflammatory cytokine production and ischemia reperfusion. Therefore, the safety of living donors requires protecting hepatic and renal functions. An optimal anesthetic technique has not been established for the maintenance of anesthesia in live liver donors.

Volatile anesthetic agents cause a reduction of hepatic blood flow. Besides, hepatic damage mechanisms cause by the biotransformation of toxic metabolites. These are the possible causes of changes in hepatocellular function, hepatic blood flow and oxygenation. On the other hand, it has been shown that volatile anesthetics reduce ischemia reperfusion injury during liver resection.

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Beck-Schimmer et al. [6] also demonstrated the protective effect of volatile agents in patients undergoing liver resection. Although both anesthetic methods can be considered safe, several studies have shown better results with volatile agents in postoperative liver and kidney functions than those with propofol-based Total Intravenous Anesthesia (TIVA). These results indicate that inhaled anesthesia may be a more appropriate anesthetic choice in patients undergoing liver resection. However, inhalation anesthetics have been shown to reduce Total Hepatic Blood Flow (THBF) secondary to the reduction of cardiac output, and dose-dependent alterations in portal venous and hepatic artery vascular resistance [7]. Another concern was that Compound A is the result of the metabolism of volatile agents and most of the studies on the kidney have been emphasized, but several studies have shown that Compound A can be hepatotoxic by transient increase in postoperative liver function tests. Several interventions have been investigated to reduce the incidence of post reperfusion syndrome during liver transplantation. However, the effect of volatile anesthetics on the incidence of post reperfusion syndrome has not been clarified yet.

Desflurane

Desflurane is metabolized by cytochrome P450 in only a very small amount (0.02%) [8]. The autoimmune antibody response inducing hepatic necrosis occurs in response to neo-antigens on trifluoro acetylated proteins that are products of cytochrome P450 dependent biotransformation. Antibody production is associated with a relative metabolic rate of each volatile agent except sevoflurane. The rate is about 15% to 40% for halothane, 2.5% for enflurane, 0.2% for isoflurane and 0.02% for desflurane. Therefore, the formation of auto-antibodies is expected to occur less frequently with isoflurane and desflurane [9]. In several studies, desflurane's effect on increasing hepatic blood flow was not found different from isoflurane, whereas in an experimental study desflurane has been shown to have no effect on hepatic blood flow and hepatic functions [10]. O'riordan et al. [11] reported that total hepatic blood flow decreased with desflurane less than isoflurane. In the same study, for sevoflurane group, a significant increase was observed in Aspartate Aminotransferase (AST) during the postoperative 1st, 2nd and 3rd days and there was an increase in Alanine Aminotransferase (ALT) during 1st and 3rd days. These findings indicated that hepatocyte injury may be more frequent in sevoflurane compared to the desflurane group. Although desflurane and sevoflurane have similar pharmacokinetic properties, desflurane is thought to be a more stable agent, which is resistant to degradation by standard carbon dioxide absorbent and is exposed to minimal metabolism by the liver [12]. Toprak et al. [13] compared desflurane (n=40) and isoflurane (n=40) regarding the effect of postoperative hepatic and renal functions on the coagulation profiles. In this study, postoperative hepatic tests and INR were found to be better in desflurane group in live donors with right hepatectomy. Similarly, Ko et al. [7] found that postoperative hepatic and renal function tests were better by using desflurane with equivalent doses of sevoflurane in live donors with right hepatectomy.

Another study in which 1629 patients with right hepatectomy were evaluated retrospectively, revealed the effect of volatile agents on liver regeneration [14]. Patients were divided into two groups as sevoflurane (n=1206) and desflurane (n=423). After propensity score matching (n=403 pairs), there was no difference between early hepatic damage scores. The authors concluded that both sevoflurane and desflurane can be used safely without affecting liver regeneration and without delaying liver function recovery.

In a retrospective study evaluating the ability of volatile agents to improve ischemia-reperfusion injury in Liver Transplantation (LT); the recipient and donor data between 2001 and 2015 were evaluated. The peak ALT level in the first 7 days after transplantation was found to be lowest for desflurane (352 IU/L), followed by sevoflurane (411 IU/L) and isoflurane (481 IU/L). All groups had similar ALT and TB for 7 days after transplantation. Graft survival, early allograft dysfunction and renal dysfunction rates were statistically similar on day 1, 7 and 30 for all 3 groups, and graft survival rate was similar in the 1st year. As a result, intraoperative desflurane administration was thought to provide better hepatoprotection as compared to sevoflurane and isoflurane, resulting in lower peak serum ALT and TB levels after transplantation. Therefore desflurane may have a unique ability to induce larger protective cellular mechanisms in hepatocytes [4].

Rotation Thromboelastometry (ROTEM) is widely used in patients with cirrhosis by facilitating the diagnosis and management of hemostasis disorders. In a study, the effects of desflurane and propofol on hemostasis were evaluated in patients with cirrhotic splenectomized by ROTEM and laboratory hemostatic tests.

Thirty patients with American Society of Anesthesiologists (ASA) II-III, aged 25 to 55 who underwent splenectomy were randomly divided into two equal groups: anesthesia with desflurane 1 MAC (6%) and Target Controlled Infusion with propofol 2 µg/ml to 5 µg/ml. This study demonstrated that desflurane and propofol anesthesia were acceptable and equally effective in ROTEM and laboratory coagulation tests in cirrhotic patients with hypersplenism and thus, the use of both anesthetic agents would be considered safe in patients with a high incidence of coagulopathy [15].

In animal experiments, increased levels of TNF-α resulted in both hepatic and pulmonary damage. Thus, TNF-α led to functional degradation in other organ systems [16]. It has been shown that TNF-α and IL-1 play a role in the early stages of rejection, and that specific inhibition of cytokines may prevent allograft rejection. It has been demonstrated that preconditioning with desflurane limits NF-κB activation induced by TNF-α and leading to a cellular protective effect.

In another study, Redel et al. [17] concluded that desflurane was more effective in the preconditioning paradigm compared to isoflurane.

Sevoflurane

Sevoflurane metabolism is rapid, and fluoride appears in the first minutes of administration. Although sevoflurane is metabolised by cytochrome P450 (about 2% to 5%), this does not result in the formation of fluoroacetylated neoantigens [18]. The reduction in Total Hepatic Blood Flow (THBF) associated with sevoflurane is mainly due to the decrease in cardiac output and adversely affects hepatic oxygenation. Sevoflurane, like isoflurane, protects THBF up to 1 MAC, but THBF decreases with increased MAC.

The highest plasma concentration of fluoride after sevoflurane anesthesia is about 50 times higher than desflurane. However, many studies have shown that sevoflurane does not adversely affect hepatic function in adult surgical patients. Mild postoperative increases in liver function tests (e.g. bilirubin and transaminases) after sevoflurane anesthesia have raised the issue of safety, particularly in obese patients. In this context, the use of sevoflurane in healthy liver donors for a

long time should be carefully evaluated. Extensive hepatic resections in donor right hepatectomy may increase the likelihood of organ toxicity.

In a study of cadaveric liver transplant recipients, patients were randomized as propofol (n=48) or sevoflurane (n=50) groups [6]. Median peak aspartate transaminase level was found to be 925 IU/L (512 IU/L to 3274 IU/L) in propofol group and 1097 IU/L (540 IU/L to 2633 IU/L) in sevoflurane group. In this study, general and major complication rates were not different and an effect was observed on clinical outcomes in favor of sevoflurane group. A randomized controlled trial was performed to compare the incidence of post reperfusion syndrome between 2 commonly used volatile anesthetics, sevoflurane (n=31) and desflurane (n=31). Post reperfusion syndrome, vasoactive drug use and postoperative course were compared [19]. The rate of post reperfusion syndrome was less in the sevoflurane group compared to the desflurane group (38.7% vs. 77.4%, $P=0.004$) and less adrenaline use were recorded in the sevoflurane group (19.4% vs. 45.2%, $P=0.030$). Postoperative hospital stay and the duration of Intensive Care Unit (ICU) stay were similar.

Preconditioning with sevoflurane during hepatic transplantation has been found to improve graft function by reducing the incidence of early allograft dysfunction in steatotic liver graft recipients [20]. Inflow occlusion maneuvers reduce blood loss during liver transection in selected patients, but are potentially harmful due to ischemia-reperfusion injury. Preventive strategies include intermittent clamping, administration of a short ischemia period prior to transection (ischemic preconditioning) or pharmacological preconditioning before transection.

It is not known whether the post-resection intervention (after conditioning) provides protection. In a prospective, randomized study, sevoflurane was administered to patients in the post conditioning group for 10 minutes. Post conditioning ($P=0.044$) and intermittent clamping ($P=0.015$) significantly decreased aspartate transaminase levels compared to the control group. The risk of complications compared to the control group was 0.08 [95% Confidence Interval (CI), 0.02 to 0.36 in the post conditioning group; $P=0.001$] and 0.50 [95% CI, 0.26 to 0.96 in the intermittent clamping group; $P=0.038$]. Pharmacological post conditioning has been shown to reduce organ damage and postoperative complications and should be used in patients with prolonged continuous inflow occlusion [21]. In conclusion, this study provides evidence of pharmacologic clinical protective effects of volatile agents on ischemic reperfusion injury in patients undergoing liver resection. Pharmacological post conditioning with volatile agents not only reduces the level of liver damage after resection, but also improves clinical outcomes. This strategy may be a new and easily applicable treatment option for patients who require long-term flow obstruction, especially during the reperfusion phase of ischemia injury.

Isoflurane

Isoflurane, an enflurane isomer, undergoes a minimum biotransformation of only 0.2%. Although this biotransformation rate is considered to be minimal, in some studies, isoflurane exhibits postoperative transaminitis as the cause of a wide spectrum of hepatic injury ranging from fulminant hepatic failure to death. Isoflurane has been shown to have a positive effect on hepatic blood supply, probably due to vasodilation directly in the hepatic vascular bed. The exact mechanism is still being investigated, but isoflurane, like sevoflurane,

has been shown to induce the regulation of hem oxygenase-1 (HO-1). This enzyme catalyzes the conversion of hem to biliverin IX, free iron and carbon monoxide, and thus can cause hepatoprotective effects by reducing portal vascular resistance. The induction of HO-1 appears to be a distinct feature of isoflurane and sevoflurane because the regulation of HO-1 was not observed with desflurane. The effects of isoflurane on hepatic blood flow are lower than sevoflurane and halothane.

In a retrospective study of live donors with right hepatectomy, hepatic and renal functions were compared between 1 MAC desflurane (n=32) and isoflurane (n=32) [7]. Postoperative bilirubin levels were lower and GFR levels were higher in Isoflurane group at 1,5,7 and 30th days. Postoperative complication rates were similar between groups, and no patient developed hepatic or renal failure. In this study, better postoperative hepatic and renal function tests were recorded among live donors in isoflurane group than desflurane. The cause of this result was particularly attributed to the increase in the rate of well oxygenated blood through the hepatic artery by isoflurane.

Merin et al. [22] showed that the blood flow of the hepatic artery was increased with isoflurane and that it could be maintained at normal level with equivalent doses of desflurane. End-stage liver disease is characterized by severe coagulopathy and bleeding is common during liver transplantation (LTx).

In another study, the effects of sevoflurane and isoflurane on clotting function, blood loss and transfusion requirement were evaluated in living donor liver transplant recipients [23]. A total of 32 patients with MELD score between 12 and 18 scheduled for transplantation, were randomly assigned to the sevoflurane (n=18) or isoflurane group (n=14). The duration of bleeding was significantly longer in sevoflurane group ($P=0.04$) during hepatectomy. INR, aPTT, PT, Factor V, Factor VII and platelet count, blood loss and transfusion requirements were similar in both groups.

Propofol

Postoperative coagulation, Glomerular Filtration Rate (GFR) and albumin levels were found to be superior to isoflurane in patients undergoing hepatectomy after propofol administration. However, both agents had been shown to be safe [24].

A retrospective study included 419 consecutive liver transplantations between 2005 and 2013 and analyzed the incidence of primary graft dysfunction and the possible association with volatile agents. The incidence of primary graft dysfunction was similar in groups: 43.2% vs. 39.1% for propofol and sevoflurane groups respectively [2].

In another retrospective analysis of 111 patients undergoing liver transplantation, total norepinephrine use was found to be lower in TIVA (n=66) than desflurane group. Besides, blood lactate level was also higher in desflurane group.

The recovery time in TIVA was found less than desflurane group (54.0 ± 33.4 min vs. 95.0 ± 78.3 min, $P=0.034$). The results of this study suggest that propofol-based TIVA may provide better hemodynamic status in anhepatic stage during liver transplantation [25].

Nuclear factor NF- κ B is an important transcription factor in oxidative stress and inflammatory response [26]. Various genes in the activation of NF- κ B induce cytokines (e.g. tumor necrosis factor or interleukin-6), chemokines and adhesion molecules. Furthermore,

NF- κ B is also a central transcription factor in TNF- α or endotoxin-induced responses. In fact, in an animal model of acute myocardial IR injury, weakening of NF- κ B activation and then down-regulation of NF- κ B were reported by volatile anesthetic preconditioning (APC). In particular, the induction of cytokine release (TNF- α , IL-1 and IL-8) and adhesion molecules (ICAM-1 and VCAM-1) is induced by NF- κ B, which causes adhesion, is regulated and accumulates in the neutrophils, resulting in large tissue damage.

Desflurane may also inhibit the second phase of the inflammatory response. In this study, it was shown that desflurane preconditioning may limit TNF- α -induced NF- κ B activation. The expression of TNFR1 on the cell surface has been shown to be unaffected by desflurane [27].

Conclusion

As a result, positive results in the studies are in favor of desflurane with less metabolism but further comparative studies are needed for patients undergoing liver transplantation.

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